Feedback from operational stakeholders who manage or respond to outbreaks is that they are often too busy to review literature or obtain relevant background information to assist them with acute response. Unlike a traditional analytical outbreak investigation report, ***Watching Briefs*** *are intended as a rapid resource for public health or other first responders in the field on topical, serious or current outbreaks, and provide a digest of relevant information including key features of an outbreak, comparison with past outbreaks and a literature review. They can be completed by responders to an outbreak, or by anyone interested in or following an outbreak using public or open source data, including news reports.*

Watching brief	
Title	Report of Monkeypox cases in 2018 in the United Kingdom
Authors	Mohana Priya Kunasekaran, Biosecurity Program, The Kirby Institute, The University of New South Wales
Date of first report of the outbreak	8 September 2018
Disease or outbreak	Monkeypox, an orthopox virus which usually causes disease in non-human primates but can occasionally infect humans. Endemic areas include the Democratic Republic of Congo and outbreaks have occurred in rural rainforest areas of Congo Basin and West Africa.
Origin (*country, city, region*)	United Kingdom
Suspected Source (specify food source, zoonotic or human origin or other)	The first case of monkeypox recorded in the UK and in the European Union (EU) was on 8 September 2018, in a Nigerian resident residing at a naval base in Cornwall, UK (1, 2). The patient was suspected to have been infected in Nigeria before travelling to the UK.
Date of outbreak beginning	7 September 2018
Date outbreak declared over	5 December 2018 (3)
Affected countries & regions	Nigeria, United Kingdom
Number of cases (specify at what date if ongoing)	There were 3 cases diagnosed in the UK between 8 and 26 September 2018. All known close contacts were followed up after their last contact with cases; no further cases were identified and no further transmission of virus was detected (3).

Clinical features	The clinical symptoms are similar to smallpox but less severe. In this outbreak, most of the suspected cases were reported to have rash (4). Monkeypox is a self-limiting disease with symptoms lasting from two to three weeks. Severity is associated with the infectious dose of exposure and patient health status and is typically worse among children. The incubation period is usually 6 to 16 days. The infectious period can be divided into two periods(4-6): 1. The invasion period: fever, headache, swelling of lymph node (distinctive feature), back pain, myalgia, fatigue 2. The skin eruption period (within 1-3 days after appearance of fever): various stages of rash, spreading from face to palms and soles of the feet, which are the most affected areas. The rash continues to evolve from maculopapules to vesicles to pustules, and eventually crusts occur in 10 days. It may take three weeks before resolution of crusts.
Mode of transmission (dominant mode and other documented modes)	Zoonotic transmission: transmission may occur from close contact with infected rodents or primates through bites and scratches or consumption of infected and inadequately cooked animal products. Infection by inoculation can occur though contact with cutaneous or mucosal lesion on animals, especially when there are breaches in the skin barrier. Person to person transmission: Transmission occurs through direct contact with blood, bodily fluids, fluids from cutaneous or mucosal lesions of infected persons or via the respiratory route through infected respiratory tract secretions. Vertical transmission is also described. Congenital monkeypox can occur as the virus is transmitted across the placenta. Similar to smallpox, there is no evidence of pre-symptomatic transmission; transmission occurs while symptomatic during the rash stage. Observational studies in the mid-1980s showed the main infectious period to be during the first week of the rash, similar to smallpox(7). A study conducted in the US in 2003 examining health care worker exposure to patients with confirmed monkeypox showed that human to human transmission in an outbreak setting is rare but possible(8). In the 2003 multistate outbreak in the US, two cases were reported to have close contact with lesions and ocular drainage of infected people, however they also had contact with the infected animals (9, 10). Person-to-person transmission could not be excluded in this instance (11, 12). In the 2017 Nigerian outbreak, three family clusters were found, which suggest some level of human-human transmission, however most patients had no obvious epidemiological linkage or human to human transmission (13). Zoonotic source of outbreak is also unclear(13). Human-to-human transmission occurs occasionally from primary cases but very rarely from secondary cases. About 7% of 149 contacts investigated in 2017 Nigeria outbreak was due to human-human transmission (14) while evidence of

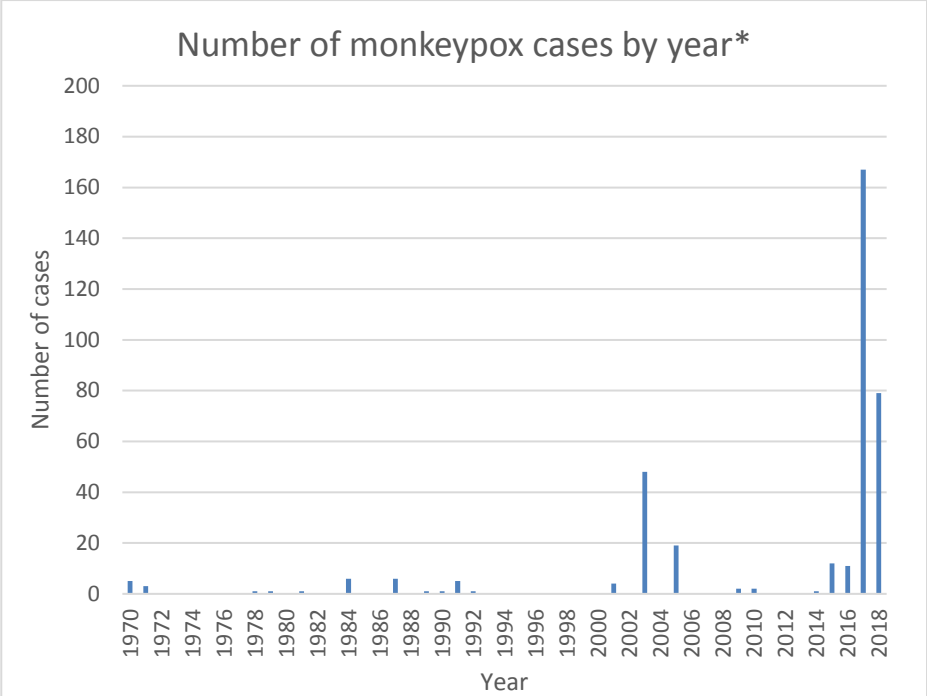
	human-human transmission observed amongst sporadic cases in Nigeria in 2018 has been acknowledged but not specifically reported (15).
Demographics of cases	The index case was a Nigerian resident living at a naval base in Cornwall, UK (1, 2). The patient was suspected to have been infected in Nigeria before travelling to the UK. No epidemiological link between the first two cases in the UK has been found (16). A 2nd case, an UK resident was confirmed on 11 September 2018, following a history of recent travel to Nigeria and presented at Blackpool Victoria Hospital. The case was transferred to high consequence infectious disease facility at Royal Liverpool Hospital once diagnosis was confirmed (17). The 3rd case, a 40 year old female healthcare assistant, was confirmed on 26 September 2018 and was involved in the care of the case in Blackpool Victoria Hospital prior to a diagnosis of monkeypox (17). The case was isolated and received treatment at Specialist unit at Royal Victoria Infirmary in Newcastle.
Case fatality rate	From previous outbreaks, the CFR has been between 1-10% (18). Two genetic clades of monkeypox virus, the West African Clade and Congo Basic clade, have been defined in the literature. According to available data, the Congo basic clade in more common than the West African clade and is endemic to the DRC (19). The West African Clade is associated with milder disease and fewer deaths and has a CFR <1%, while the Congo Basin clade has CFR up to 11% and previously documented human-human transmission (20). In September-December 2017, the West African clade was identified in the Nigerian outbreak and, based on NCDC data, had a CFR of 2.9% with 68 confirmed cases from 197 suspected cases across 22 states (14). In 2018, based on NCDC data, the CFR was 2.2% with 45 confirmed cases from 114 suspected cases across 13 states. The same West African clade was reported (15).
Complications	Complications include permanent scarring, disfigurement and death. The prognosis may be worse for patients who are younger, have other co-morbidities such as malnutrition, or those who are immunocompromised.
Available prevention	There is no vaccine for monkeypox. Vaccination against smallpox confers cross-protection for monkeypox and has been shown to be 85% effective against monkeypox (21). The vaccine is available as part of the national stockpile in the UK and the government was reported to have ordered more. The vaccine is currently not publicly administered or available in Nigeria (22).

	Patients and contact tracing activities are managed by public health authorities and Nigeria Centre for Disease control, especially in states with confirmed cases, and by the High Consequence infectious Diseases (HCID) Network in the UK. Recommendations for infection prevention and control measures: • Contact tracing precautions in healthcare setting • Appropriate use of personal protective equipment • Proper hand hygiene • Safe handling of meat products • Avoid close contact with possible source of infections • Vaccination of healthcare workers in the frontline and contacts of cases(23)
Available treatment	Treatment is supportive and based on the patient's clinical condition. Symptomatic relief is also provided and vaccine-immune globulin can also be used (24). Tecovirimat is the only approved antiviral treatment by the US Food and Drug Administration and can be a treatment option for monkeypox infection (25, 26). Antiviral treatment using cifdofivir, NIOCH-14, CMX-001 and Tecovirimat (ST-246) are in various stages of clinical trials (27).
Comparison with past outbreaks	Two previous outbreaks were reported in Nigeria in 1971 and 1978, with two cases and one case respectively amongst individuals who were not vaccinated against smallpox. Cases were linked to consumption of meat obtained from tropical rainforests (28). The outbreak in 1971 involved a four-year-old female index case. The secondary case was her 24-year-old mother. The single case identified in 1978 was a 35 year old man (28). Since then monkeypox has remained a disease of Central and West African countries, except in 2003 when 37 confirmed and 10 probable cases were reported across six states in the US, the first reported outbreak outside of Africa. Those affected had close contact with pet prairie dogs (rodent of Cynomys species) imported from the endemic region (29). Prior to 2017, the largest outbreak ever reported in Africa was in 1996 in the Democratic Republic of Congo, with more than 70 cases and lasting for one year(30). This was associated with close contact with squirrels and some person to person transmission. The ongoing Nigerian outbreak in 2018 has significantly more cases than previous outbreaks, when probable and confirmed cases are included. Between the start of the outbreak in September 2017and 31 August 2018, 262 suspected cases were reported from 26 states. Of these, 113 were confirmed in 16 states, with seven deaths (2). The first outbreak was not declared over, and

	sporadic reporting of cases continued in 2018. From September to December 2017, there was 68 confirmed and 197 suspected cases across 22 states (14). The end of outbreak was not declared; there was continued reporting of sporadic case of monkeypox in 2018. Since the beginning of 2018, 76 monkeypox cases including 2 deaths were reported in 15 states (2). Preliminary genetic sequencing suggest multiple sources of introduction and no epidemiological linkages across states (14, 15).
Unusual features	• The UK outbreak is only the second outbreak outside of West and Central Africa. The first outbreak was the multistate outbreak in the United States of America, but that was due to contact with imported animals. • The source of infection for the 1st and 2nd cases is unknown. • The two cases originating from Nigeria were apparently unrelated. • Importation of two cases to the UK from Nigeria through travel within days of each other, but unrelated. • From January to September 2018, there were only 76 confirmed and 114 suspected cases of monkeypox in Nigeria, September being the time of the UK outbreak. This makes the probability of two unrelated cases occurring in the UK in people coming from Nigeria (and presumably exposed in Nigeria) fairly low.
Critical analysis	This outbreak started with imported cases in the UK, most likely exposed in Nigeria. There is no epidemiological linkage amongst cases across states in Nigeria, indicating separate source of the two cases in Nigeria. Overall the likelihood of monkeypox spreading in Europe through the UK remains low, because the human to human transmission is not the predominant mode of transmission, but more travel-related cases cannot be excluded as there is an ongoing reporting of sporadic cases in Nigeria and other parts of Central and West Africa since its re-emergence in September 2017 (2). There is a need for a trained workforce on both sides to be aware of symptoms, especially for physicians to be aware of similarities with and differences from varicella and orthopoxvirus infections. The second case was not initially diagnosed, despite there being a prior case of monkeypox diagnosed in the UK, highlighting failures of triage and diagnosis in the clinical setting – in this case resulting in nosocomial infection of a nurse. Heightened surveillance at airports may ensure early detection and efficient control of spread (31). The risk of new cases of monkeypox appearing in the UK depends on the extent of the circulation of the virus in Nigeria and in other countries of West and central Africa (32). Given the current size of the epidemic, it is a low risk. It would also be advisable for health care professionals and public health officials to be aware of the outbreak situation in the Western and Central African region, especially Nigeria. The risk of transmission person to person depends on the nature and duration of contact. Generally, monkeypox has a low person to person transmission potential, with six being the highest number of suspected consecutive

	transmission events recorded and varied incubation periods, depending on differences in nature and duration of exposure (33). The household attack rate from previous studies ranged from 3% to 11% and higher among unvaccinated persons and up to 6 intrafamily transmission events have been documented (21, 34, 35). The median household attack rate was as high as 50% in one study, which could have been due to underestimating the total number of human monkeypox cases and bias introduced as interviews were done by households (36). No close contacts of the three UK cases were reported to have monkeypox in this current outbreak, but the third case was a nurse who became infected while caring for a patient who was the second imported case. The first two cases have no epidemiological link. No isolated cause can be singled out for the nurse acquiring the disease from the second case, although this occurred prior to the diagnosis of monkeypox being made. Multiple factors, such as inappropriate PPE, low risk perception and delayed identification and diagnosis of case, have contributed to this. However, this case triggered the systems developed in the wake of the Ebola 2014 crises to prepare for a fatal infectious disease entering the UK (17). Once a HCID such as monkeypox has been confirmed by appropriate laboratory testing, cases in the UK are transferred to designated HCID treatment centre as soon as possible and highly probable cases are also moved to the treatment centres (23). Once diagnosis was confirmed, the cases in this UK outbreak were transferred to and managed by hospitals that were designated to provide support and one of two principal HCID treatment centres respectively (23). Effective communication, accurate risk assessment and implementation of response activities mitigated the outbreak and proved that the current contingency planning efforts are appropriate (17, 23). However, the cases are too few to make any comment about the robustness of the system. Cases could have been missed and the strain may have been introduced into the UK animal population, although this is unlikely. Most of the available data on monkeypox comes from individual case outbreak reports and passive ad-hoc surveillance. It is uncertain on how well this reflects the actual epidemiology of monkeypox.

Figure 1. Number of monkeypox cases globally by year



**Excluding the cases occurring in the Democratic Republic of Congo >1000/year from 1970 (37). Data obtained from published studies (32, 37)*

The number of monkeypox cases has been increasing in the last two decades in more countries beyond the endemic area of Democratic Republic of Congo and West Africa (32)(37) (Figure 1). As most of the current contemporary population has not been previously vaccinated against smallpox, there is possibly a large susceptible population to monkeypox virus infection in Nigeria and the UK. A possible explanation for the rise in monkeypox cases could be waning immunity due to smallpox vaccine cessation since the 1980's. The highest number of cases in the Nigerian September 2017 outbreak was seen in the 21-30 age group, those born between 1987 and 1996, coinciding with being born after smallpox vaccine cessation (38). As most of the current population has not been previously vaccinated against smallpox, and more with contraindication against the vaccine, there is possibly a large susceptible population to monkeypox virus infection in Nigeria and the UK. Cross-protective effect of smallpox vaccine is being further explored through ongoing studies which also show effectiveness of third and fourth generation smallpox vaccines against monkeypox (39, 40). The vaccine against smallpox in humans has been shown to be 85% effective against monkeypox (21) but issues with vaccine safety and relatively small numbers of cases have not justified vaccination. Further, monkeypox is occurring in areas which struggle to maintain adequate vaccine coverage levels for routine vaccinations against measles and polio, which remain a higher priority (41). The global increase in monkeypox should be a cause of concern.

Key questions	Why have travel-related cases only occurred in the UK to date? What is the probability of two unrelated cases coming from Nigeria to the UK within days of each other, when total case numbers in Nigeria were around 100 at that time? What was the risk of cross-border transmission to other countries from Nigeria? Which strain of monkeypox was introduced to UK? Is this strain likely to circulate in animal reservoirs? What is the phylogenetic relationship of the UK strains to past and present Nigerian strains? Does the rate of waning of smallpox vaccine-induced immunity and the rise in unvaccinated cohorts in West Africa correlate to the rise in monkeypox incidence?
References	1. Nakaji S, Parodi S, Fontana V, Umeda T, Suzuki K, Sakamoto J, et al. Seasonal changes in mortality rates from main causes of death in Japan (1970--1999). Eur J Epidemiol. 2004;19(10):905-13. 2. European Centre for Disease Prevention and Control (ECDC). Rapid risk assessment: Monkeypox cases in the UK imported by travellers returning from Nigeria, 2018 2018 [updated 21 September 2018. Available from: https://www.ecdc.europa.eu/sites/portal/files/documents/13-09-2018-RRA-Monkeypox-Nigeria-United-Kingdom.pdf. 3. Public Health England (PHE). Monkeypox case in England: GOV.UK; 2018 [updated 5 December 2018. Available from: https://www.gov.uk/government/news/monkeypox-case-in-england. 4. EDIS R. Epidemic Hazard in Nigeria 2017 [Available from: http://hisz.rsoe.hu/alertmap/database/?pageid=event_update&edis_id=EH-20171004-60073-NGA. 5. Pal M, Mengstie F, Kandi V. Epidemiology, Diagnosis, and Control of Monkeypox Disease: A comprehensive Review. American Journal of Infectious Diseases and Microbiology. 2017;5(2):94-9. 6. Parker S, Nuara A, Buller RML, Schultz DA. Human monkeypox: an emerging zoonotic disease. Future microbiology. 2007;2(1):17-34. 7. Jezek Z, Marennikova S, Mutumbo M, Nakano J, Paluku K, Szczeniowski M. Human monkeypox: a study of 2,510 contacts of 214 patients. Journal of infectious diseases. 1986;154(4):551-5. 8. Fleischauer AT, Kile JC, Davidson M, Fischer M, Karem KL, Teclaw R, et al. Evaluation of human-to-human transmission of monkeypox from infected patients to health care workers. Clinical Infectious Diseases. 2005;40(5):689-94. 9. Langkop C, Austin C, Dworkin M, Kelly K, Messersmith H, Teclaw R, et al. Multistate outbreak of monkeypox-Illinois, Indiana, Kansas, Missouri, Ohio, and Wisconsin, 2003. Morbidity and Mortality Weekly Report. 2003;52(24):561-3. 10. Control CfD, Prevention. Update: multistate outbreak of monkeypox--Illinois, Indiana, Kansas, Missouri, Ohio, and Wisconsin, 2003. MMWR Morbidity and mortality weekly report. 2003;52(25):589.

11. Reed KD, Melski JW, Graham MB, Regnery RL, Sotir MJ, Wegner MV, et al. The detection of monkeypox in humans in the Western Hemisphere. New England Journal of Medicine. 2004;350(4):342-50.
12. Guarner J, Johnson BJ, Paddock CD, Shieh W-J, Goldsmith CS, Reynolds MG, et al. Monkeypox transmission and pathogenesis in prairie dogs. Emerging infectious diseases. 2004;10(3):426.
13. Yinka-Ogunleye A, Aruna O, Ogoina D, Aworabhi N, Eteng W, Badaru S, et al. Reemergence of Human Monkeypox in Nigeria, 2017. Emerging infectious diseases. 2018;24(6):1149.
14. Nigerian Centre for Disease Control (NCDC). Situation Report 013 Week 51 Monkeypox Outbreak in Nigeria Nigeria2017 [updated 22 December 2017. Available from: https://ncdc.gov.ng/diseases/sitreps/?cat=8&name=An%20Update%20of%20Monkeypox%20Outbreak%20in%20Nigeria.
15. Nigerian Centre for Disease Control (NCDC). Nigeria Monkeypox Situation report 028. Nigeria2018 [updated December 2018. Available from: https://ncdc.gov.ng/diseases/sitreps/?cat=8&name=An%20Update%20of%20Monkeypox%20Outbreak%20in%20Nigeria.
16. Public Health England (PHE). Monkeypox: Heathcare worker is third UK case of disease: BBS News; 2018 [updated 26 September 2018. Available from: https://www.bbc.com/news/uk-england-45652459.
17. Parveen N. Monkeypox cases put UK's tropical disease response to the test: The Guardian; 2018 [updated 8 October 2018. Available from: https://www.theguardian.com/society/2018/oct/07/monkeypox-cases-put-uks-tropical-disease-response-to-the-test.
18. Jezek Z, Khodakevich L, Wickett JF. Smallpox and its post-eradication surveillance. Bulletin of the World Health Organization. 1987;65(4):425.
19. Mwamba DK KB, Shongo RL, Pukuta E, Kayembe NJM. Profil épidemiologique du monkeypox en RDC, 2010-2014 Monkeypox in DRC, epidemiological profile: 2010-2014. Ann African Med. 2014;8:1855-60.
20. Ježek Z, Szczeniowski M, Paluku K, Mutombo M. Human monkeypox: clinical features of 282 patients. Journal of infectious diseases. 1987;156(2):293-8.
21. Fine P, Jezek Z, Grab B, Dixon H. The transmission potential of monkeypox virus in human populations. International journal of epidemiology. 1988;17(3):643-50.
22. Lynch M. UK orders smallpox vaccine in response to monkeypox cases: in-Pharmatechonologist.com; 2018 [updated 24 September 2018. Available from: https://www.in-pharmatechnologist.com/Article/2018/09/24/UK-orders-smallpox-vaccine-in-response-to-monkeypox-cases.
23. Vaughan A, Aarons E, Astbury J, Balasegaram S, Beadsworth M, Beck CR, et al. Two cases of monkeypox imported to the United Kingdom, September 2018. Eurosurveillance. 2018;23(38).
24. Adalja AA, Toner E, Inglesby TV. Clinical management of potential bioterrorism-related conditions. New England Journal of Medicine. 2015;372(10):954-62.
25. Hoy SM. Tecovirimat: First Global Approval. Drugs. 2018;78(13):1377-82.
26. Russo AT, Grosenbach DW, Brasel TL, Baker RO, Cawthon AG, Reynolds E, et al. Effects of Treatment Delay on Efficacy of Tecovirimat Following Lethal Aerosol Monkeypox Virus Challenge in Cynomolgus Macaques. The Journal of infectious diseases. 2018;218(9):1490-9.

27. Kabuga AI, El Zowalaty ME. A review of the monkeypox virus and a recent outbreak of skin rash disease in Nigeria. Journal of Medical Virology. 2018.
28. Breman JG, Kalisa-Ruti M, Zanotto E, Gromyko A, Arita I. Human monkeypox, 1970-79. Bulletin of the World Health Organization. 1980;58(2):165.
29. Reed K, Melski J, Graham M, Jezek Z, Grab B, Dixon H, et al. Monkeypox in the Western hemisphere. N Engl J Med. 2004;2004(350):1790-1.
30. Kantele A, Chickering K, Vapalahti O, Rimoin A. Emerging diseases—the monkeypox epidemic in the Democratic Republic of the Congo. Clinical Microbiology and Infection. 2016;22(8):658-9.
31. Gubler DJ. The global threat of emergent/re-emergent vector-borne diseases. Vector Biology, Ecology and Control: Springer; 2010. p. 39-62.
32. Sklenovská N, Van Ranst M. Emergence of monkeypox as the most important orthopoxvirus infection in humans. Frontiers in public health. 2018;6.
33. Learned LA, Reynolds MG, Wassa DW, Li Y, Olson VA, Karem K, et al. Extended interhuman transmission of monkeypox in a hospital community in the Republic of the Congo, 2003. The American journal of tropical medicine and hygiene. 2005;73(2):428-34.
34. Formenty P, Muntasir MO, Damon I, Chowdhary V, Opoka ML, Monimart C, et al. Human monkeypox outbreak caused by novel virus belonging to Congo Basin clade, Sudan, 2005. Emerging infectious diseases. 2010;16(10):1539.
35. Reynolds MG, Yorita KL, Kuehnert MJ, Davidson WB, Huhn GD, Holman RC, et al. Clinical manifestations of human monkeypox influenced by route of infection. The Journal of infectious diseases. 2006;194(6):773-80.
36. Nolen LD, Osadebe L, Katomba J, Likofata J, Mukadi D, Monroe B, et al. Extended human-to-human transmission during a monkeypox outbreak in the Democratic Republic of the Congo. Emerging infectious diseases. 2016;22(6):1014.
37. Durski KN MA, Nakazawa Y, et al. . Emergence of Monkeypox — West and Central Africa, 1970–2017. MMWR and Morbidity and Mortality Weekly Report. 2018;67:306-10.
38. Nigerian Centre for Disease Control (NCDC). Situation Report (No. 006) NCDC, Nigeria; 2017 [updated 2 November 2017. Available from: http://www.ncdc.gov.ng/themes/common/files/sitreps/c1fa9b9cbdc48695e9df75225967f76f.pdf.
39. Monkeypox: Smallpox vaccines delivered to UK for healthcare workers: Outbreak News Today; 2018 [updated 20 September 2018. Available from: http://outbreaknewstoday.com/monkeypox-smallpox-vaccines-delivered-uk-healthcare-workers-58796/.
40. Petersen BW, Kabamba J, McCollum AM, Lushima RS, Wemakoy EO, Tamfum JJM, et al. Vaccinating against monkeypox in the Democratic Republic of the Congo. Antiviral research. 2018.
41. Realegeno S, Puschnik AS, Kumar A, Goldsmith C, Burgado J, Sambhara S, et al. Monkeypox Virus Host Factor Screen Using Haploid Cells Identifies Essential Role of GARP Complex in Extracellular Virus Formation. Journal of Virology. 2017;91(11):e00011-17.